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September 5, 2005

Genevieve Matanowski, MD, MPH
Chair, SAB Arsenic Review Panel
USEPA Science Advisory Board

Re: Written submission for the oral public comments section at the Arsenic Review Panel meeting on September 12, 2005

Dear Dr. Matanowski,

I am writing in response to charge C2 in the final 7/25/05 charge to EPA Science Advisory Board Arsenic Review Panel:

> ***C2:*** *Use of human epidemiological data from direct iAs exposure*
>
> ***Question 1:*** *Does the Taiwanese dataset remain the most appropriate choice for estimating cancer risk in humans? What is the rationale for the response*?
>
> ***Answer:*** NO

Rationale

The Taiwanese dataset [data underlying the study Wu et al. (1989) study and the analyses in Morales et al. (2000)] has been analyzed by the NRC (1999; 2001) and the EPA]. It has served as their analytic database for estimating the risk of internal cancers from the ingestion of water containing inorganic arsenic. NRC considered that the reason for modeling with the SW-Taiwan data was that at that time there was insufficient information to assess the risk from low-level exposure and only the SW-Taiwan study had a sufficient quantity of data over a wide range of arsenic exposures that could be used for risk analysis and extrapolation. They considered that their findings were supported by a number of studies, including the study of Ferreccio (2000). They highlighted Chiou (2001) from NE Taiwan as having superior study design, but lacked sufficient power because of its short follow-up period.

In general, there is agreement that high arsenic exposure is a risk factor for internal human cancers. Nonetheless, there is considerable disagreement as to whether low arsenic exposure levels is a risk factor for internal human cancers (~ <= 100 ug/L). Since the NRC reports, a number of studies have been published that did not find an increase of internal cancers at low level arsenic exposure. These include Guo (2000),

Steinmaus (2003), Lamm (2003, 2004), and Bates (2004), all of which found no evidence of an increase in bladder cancer rate at low-level arsenic exposure levels. Both Guo (2004) and Chen CL (2004) found no increase in lung cancer rate at low-level arsenic exposure levels.

The question is, however, whether currently the Wu dataset is the most appropriate for analysis of human carcinogenesis from arsenic ingestion. The major issue of concern in the Wu dataset is the validity of the exposure metric. We have presented below a number of analyses and discussion that suggest that there are unaccounted biases or unidentified factors that inhibit a straight-forward dose-response analysis.

Further Analysis of the SW-Taiwan Dataset

Exposure metric

The Wu study used the median village well arsenic concentration as it's only metric of exposure. Historically, exposure metrics in the Blackfoot Disease (BFD) endemic area where the Wu study was conducted have also included water source (proportion of village wells that tapped the artesian aquifer) and/or township of residence.

The underlying data on village well arsenic levels for the Wu dataset can be found in the NRC (1999) Table A-10 (pages 308-309). That table gives a set of arsenic levels for the 42 villages, each of which is presumably the median of the measures of that well for each of the wells in the village. For about half of the villages (20/42 = 48%), there was apparently only one well. The exposure metric for each village is then the median of this village-specific set of arsenic levels where there are multiple wells or the single value where there is only one well reported. While the derivation of the village-specific median is quite transparent, there has been considerable question as to whether the median village well arsenic level is the appropriate metric of the villager's arsenic-containing drinking water ingestion and whether the given data accurately reflect the water ingested by the residents. This has been extensively analyzed and reported by Brown and Chen (1995) and Brown and Ross (2002). We have previously published (Lamm et al., 2003) a stratified risk analysis of the Wu dataset, adding in "water source" as a second explanatory variable or metric of exposure and found that it behaved as an effect modifier.

In our August 19, 2005 report to the Arsenic Review Panel, we pointed out that Chen et al. (1985) had previously shown bladder cancer mortality was particular elevated in two of the study townships (e.g., Peimen and Hseuehchia) and that this was not dealt with in the analysis of the Wu data. We also discussed how non-representative the median might be. We then suggested that this source of uncertainty could be avoided by examining the data from the villages that had only one well. Finally, we showed from an analysis of the village-specific bladder cancer mortality rates for the one-well villages that the arsenic levels separated into two groups (< 0.15 ppm and > 0.25 ppm) yielded a strong negative association with arsenic in the lower exposure group (R^2 = 0.20) and a weak, but positive slope in the higher exposure group (R^2 = 0.02).

This distinction in lower and higher exposure groups was consistent with the description in Wu et al. (1898) that arsenic well levels formed two clusters with the lower being at 0.05-0.25 ppm. We now extend those discussions.

Associations Seen With One-Well and Multi-Well Villages

The data set relates to 42 villages - 20 one-well villages and 22 multiple-well villages - in 5 townships. The bladder and lung cancer mortality are expressed as village-specific standardized mortality ratios (SMR). The arsenic well data originate from the NRC (1999) Table A-10. The age and gender person-year and mortality distributions for each village had been provided by Prof. Ryan and by the EPA. That data set also included the SW-Taiwan cancer mortality distribution as presented Table 1 of Morales et al. (2000). The SMR based on the SW-Taiwan reference population was chosen as the outcome metric based on the recommendation in NRC (2001). They had commented with respect to the Tsai et al. (1999) study, that in Taiwan the "use of the regional and national rates as referents for mortality studies in this region is appropriate and the important confounding is unlikely when these external rates are incorporated in a quantitative risk assessment (page 67)."

The twenty one-well villages comprise 48% of the villages (20/42 = 48%) and 52% of the person-years at risk (251,311/486,959 = 52%) in the over-all Wu et al. (1989) data set. The number of wells in each village ranged from 1 to 47, with about half having only one well. There exists no information as to which well the villagers used in a multiple-well village.

In the Figures 1-6 below, we have displayed the village-specific gender-specific SMRs for bladder cancer and lung cancer by median village well arsenic level (whether based on one or multiple wells) for all study villages, the one-well villages, and the multi-well villages. We have provided a linear regression for each sub-set and focus attention on both the direction of the slope and the magnitude of explanatory power (e.g., R^2). In summary, we find that essentially all of the explanatory power appearing for the arsenic level variable in the overall study is found among the multi-well villages. Very little explanatory power is found in the models based on the data from the one-well villages.

In Figure 1, the models based on the SMRs for all the villages, the arsenic variable explains 18% of the between-village variance for the male bladder cancer mortality SMRs (p=0.006) and 10% for female bladder cancer mortality SMRs (p=0.04) Similarly, it explains 14% of the between-village variance for the male lung cancer mortality SMRs (p=0.015) and 19% of the between-village variance for female lung cancer mortality SMRs (p=0.004) [Figure 2].

Figure 1: Bladder Cancer SMRs for all 42 Villages by Gender and Median Village Well Arsenic

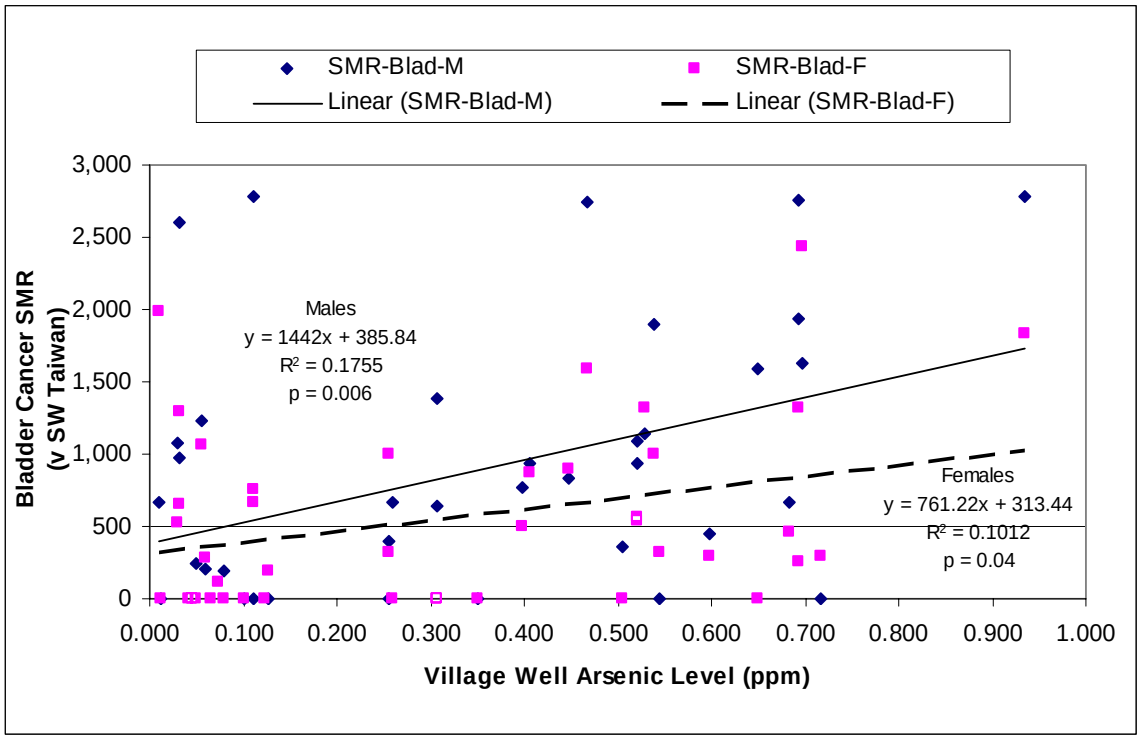
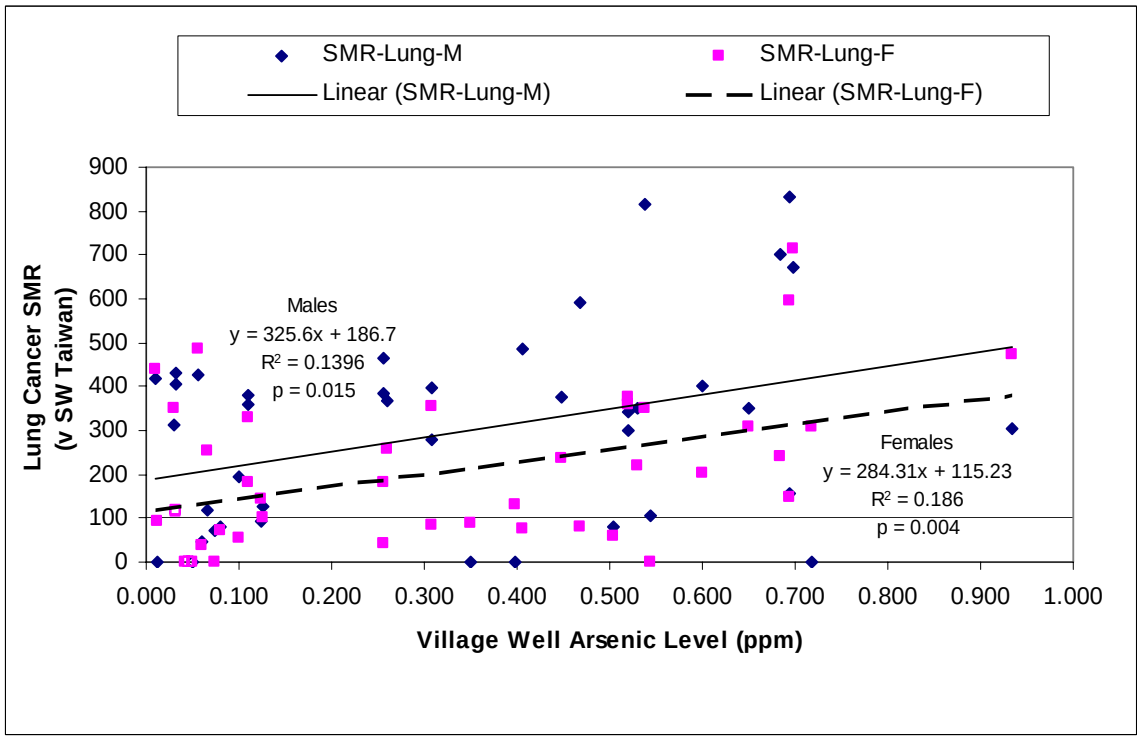


Figure 2: Lung Cancer SMRs for all 42 Villages by Gender and Median Village Well Arsenic Level



In contrast, analysis of the data from the one-well villages generally finds very little explanatory power; 5 % for the male bladder cancers (p=0.34) and less than 1 % for the female bladder cancers (p=0.75) [Figure 3] and 9% for the male lung cancers (p=0.20) and less than 1 % for the female lung cancers (p=0.88) [Figure 4].

Figure 3: Bladder Cancer SMRs for One-Well Villages by Gender and Single Village Arsenic

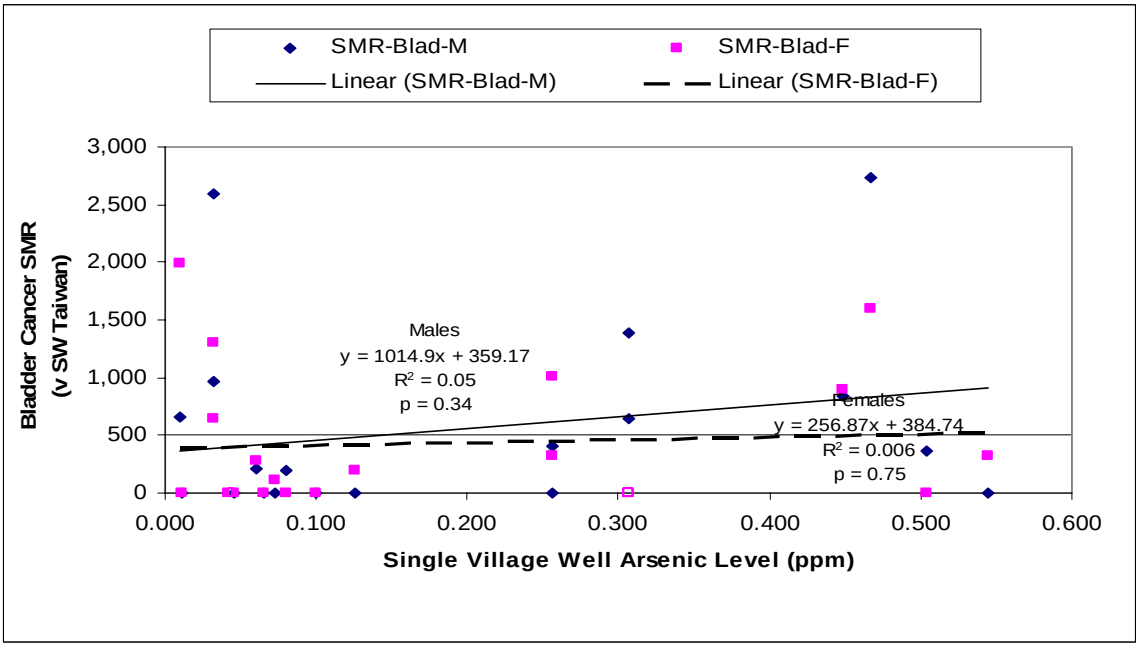
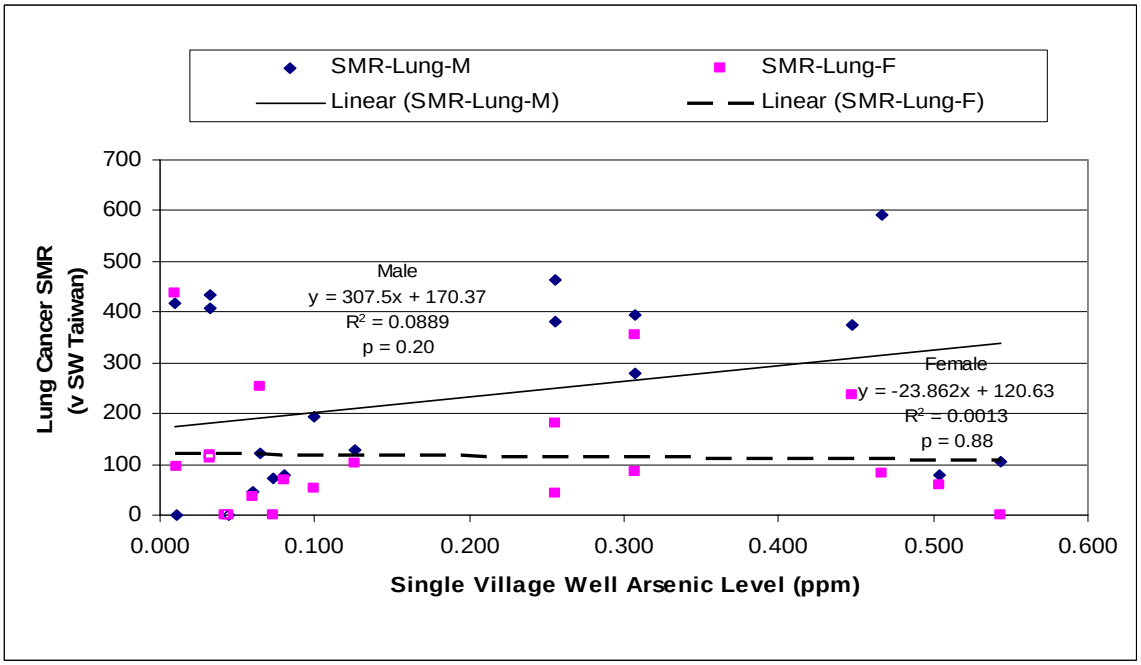


Figure 4: Lung Cancer SMRs for One-Well Villages by Gender and Single Village Arsenic Level



Figures 5 and 6, respectively, show bladder and lung cancer mortality for the 22 multiple-well villages. As indicated, similar to the all village models, among the multi-well villages, the arsenic exposure variable has R^2s of 14 % for male (p=0.08) and for female bladder cancers (p=0.08) [Figure 5] and 8 % for the male lung cancers (p=0.19) and 14 % for the female lung cancers (p=0.09) [Figure 6].

Figure 5: Bladder Cancer SMRs for Multiple-Well Villages by Gender and Median Village Well Arsenic Level

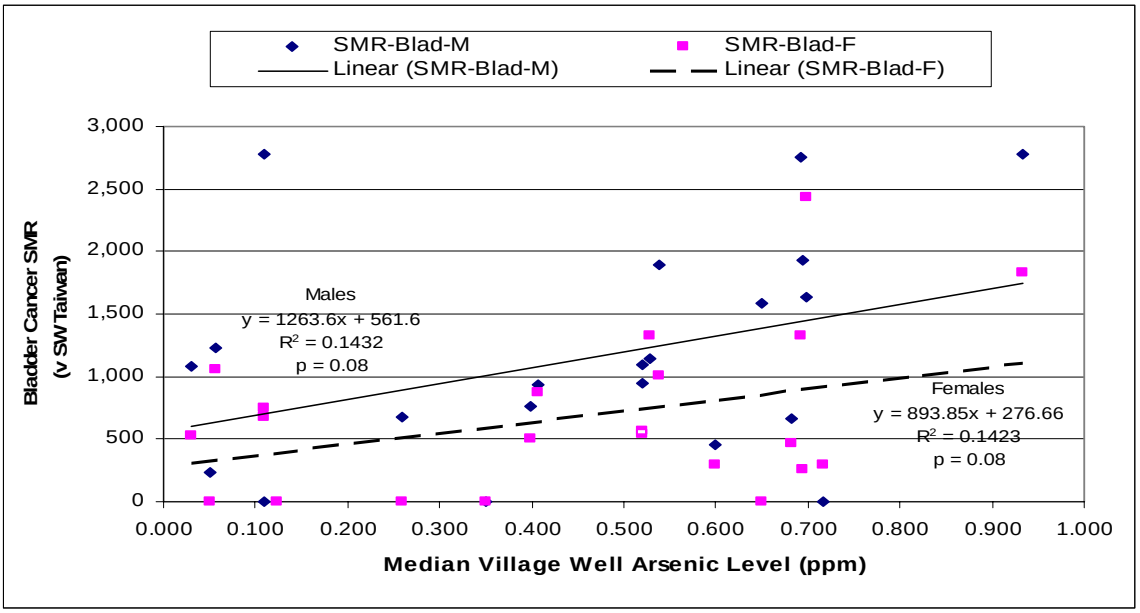
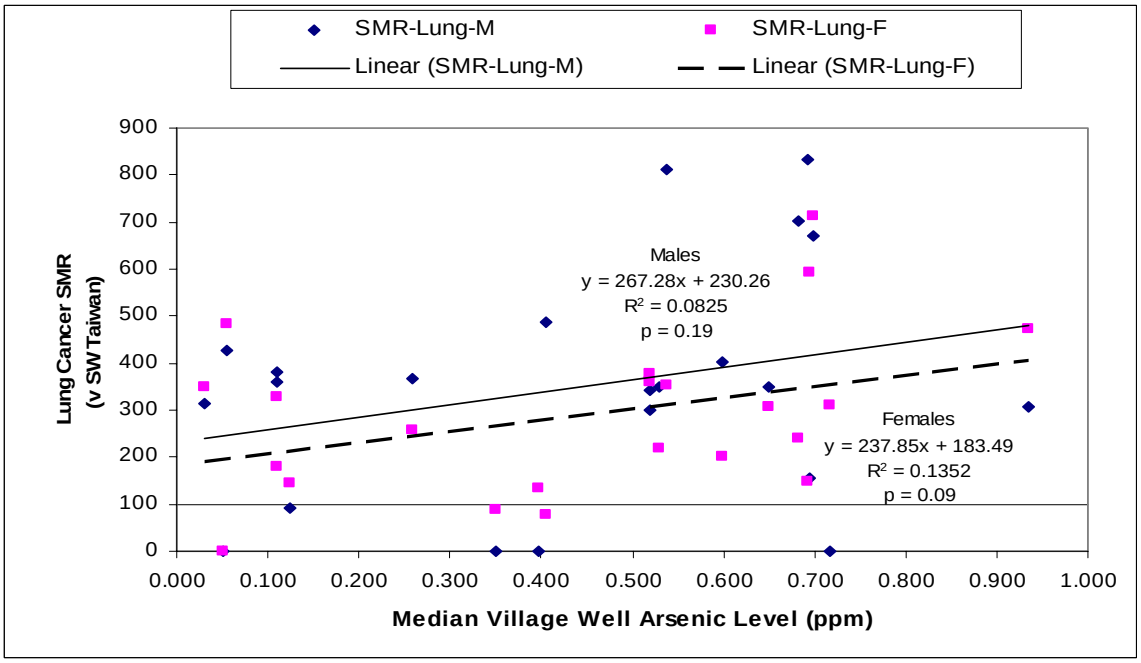


Figure 6: Lung Cancer SMRs for Multiple-Well Villages by Gender and Median Village Well Arsenic Level



It is interesting to note that only for male lung cancers is the R^2 similar for the one-well villages and the multiple-well villages. In all other cases, almost all of the strength of the association is found among the multi-well villages and almost none is found among the one-well villages. This finding is open to a number of interpretations.

One might have suggested that the reduction in explanatory power when going from a 42-village set [all villages] to a 20-village [one-well villages] set might be due to the reduction in sample size. In that case, it would be unlikely that a similar reduction in explanatory power was not seen when going from the 42-village set to a 22-village [multi-well villages] set.

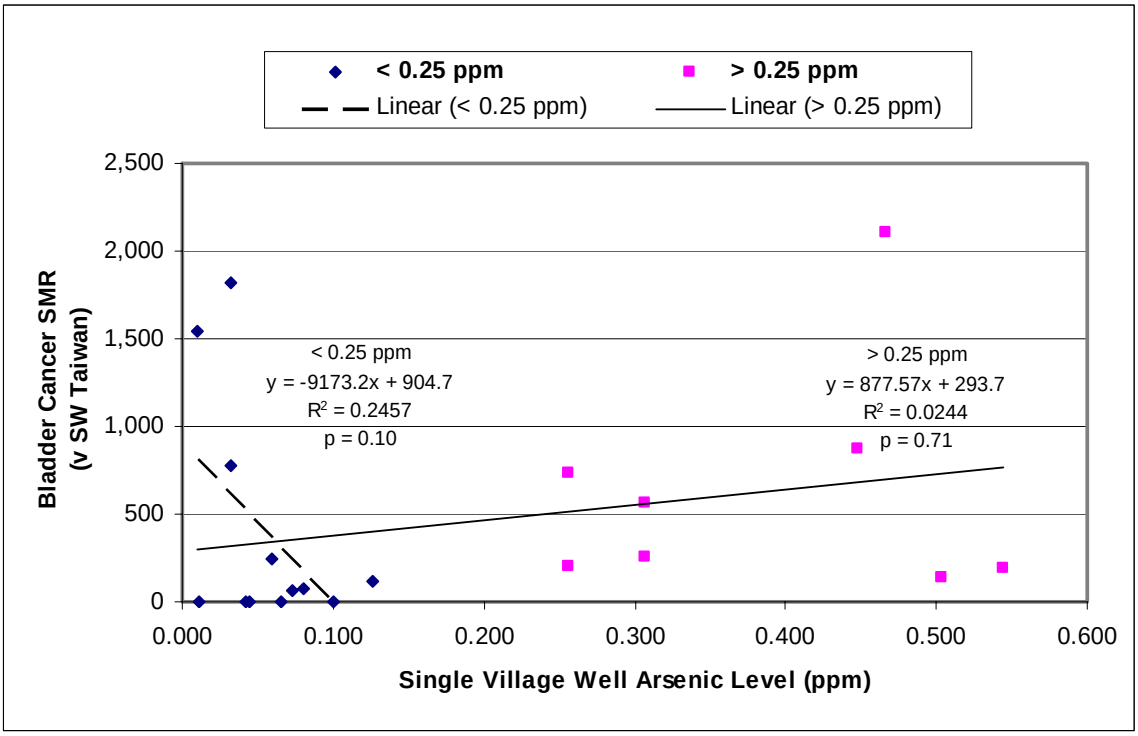
Another interpretation is that this demonstrates that the use of the median of many wells eliminates the uncertainty of accurate representation from only a single well. However, that would mean that there is marked exposure mis-assignment among half the villages. That is not a tenable explanation for a valid data set. Our *a priori* assumption had been that the use of the median introduces a source of uncertainty in exposure assignment thereby reducing any apparent association. We do not have an explanation, though this observation does raise the issue of the underlying data validity and/or its interpretation.

There are many questions regarding data quality that are raised by the above analysis. Are the diagnoses correct? Is the case count correct? Is the population ascertainment and subsequent person-year distributions correct? Is the well inventory complete and accurate? Are the arsenic measurements correct? Did the residents only drink from their village wells? Was the arsenic level constant over decades? Were the risks independent of subsequent switch to piped water both quantitatively and temporally? As the data to examine these questions is limited or absent, we have to accept various assumptions. We are struck with the observation that in multiple ways when the data is bifurcated, the dose-relationship differs in the two sections. We conclude that there exists within the data some additional unobserved factor(s) that influences the outcome, but has not been adequately identified or characterized.

Examination of Villages with Low-level Arsenic Exposures Assigned

The purpose of modeling the SW-Taiwan data has been to attempt to determine what the risks are at low-level arsenic exposure. We have chosen, therefore, to examine the data within the SW-Taiwan dataset from the villages considered to have low-level exposures. Wu et al. (1989) identified a cluster of well water arsenic levels at < 0.25 ppm. Examination of the NRC data set and its graphic presentation [Figures 1 and 2] indicate that there is a break in the exposure distribution at 0.126 ppm. As our analyses above have generally shown reasonably similar slopes for cancers in males and females, we will continue the analytic inquiry without stratifying by gender, but rather using the male and female data combined. We have returned to our analysis of the one-well village bladder cancer SMR. Figure 7 shows the one-well village data distinguishing between those with exposures above and below 0.25 ppm.

Figure 7: Bladder Cancer SMR for One-Well Villages by Single Village Well Arsenic Level

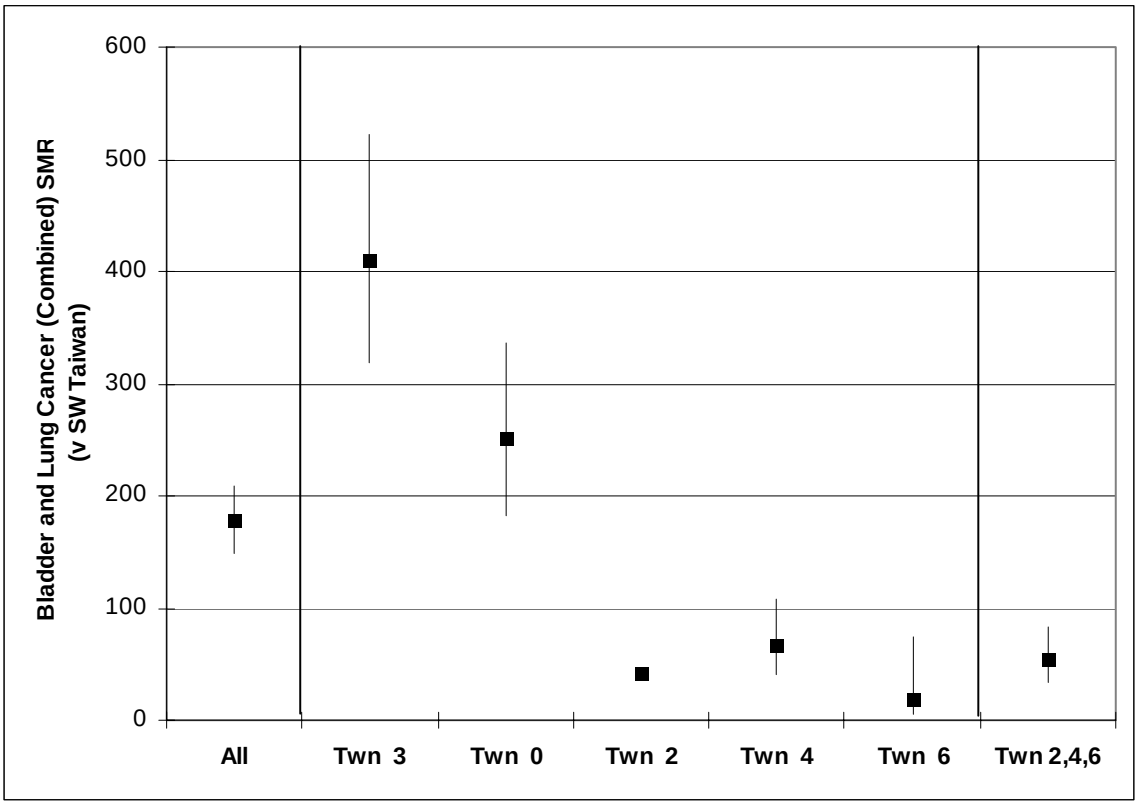


We noted that the lower level exposure villages showed a negative slope with R^2 = 0.25, which appears to be inconsistent with the general expectation of a dose-response model, though p=0.10. Furthermore, the data seem to separate into three villages with risks of about 1,000 (=/- 500) and eight villages with risks of about 100 (+/- 50). In comparing the information we had on these eleven villages, we were struck by the observation that all three of the high risk villages and none of the low risk villages had come from Township 3. We therefore returned to the analysis of the low-level arsenic exposure villages choosing to include "Township" as an explanatory variable.

Figure 8 shows the risk analysis for bladder and lung cancers (male and females combined) for the 18 low-level exposure villages. We have looked at the outcome of bladder and lung cancers together in both one-well and multi-well villages in order that our analysis not be excessively influenced by the data that led us to exam "Township" as an explanatory variable.

The NRC dataset reveals that the villages are identified as being in six townships (0, 2, 3, 4, 5, and 6) which are not otherwise identified. Neither inquiry to EPA or to the authors in Taiwan has yielded the specific code. There were no Township 5 villages among the low-level exposure villages. There were four villages each for Townships 0, 3, and 4, plus two villages from Township 6 and one from Township 2.

Figure 8: Bladder and Lung Cancer (Combined) SMRs by Township for Low-Level Arsenic Exposure Villages (<= 0.126 ppm) with 95% confidence limits



The overall SMR for these villages was 184 with a 95 % confidence interval of (153-216). Thus, overall, these villages showed a significantly increased cancer risk compared to regional rates. When the analysis was stratified by township, it was observed that both Township 3 and Township O had rates significantly greater than Townships 2, 4, and/or 6.

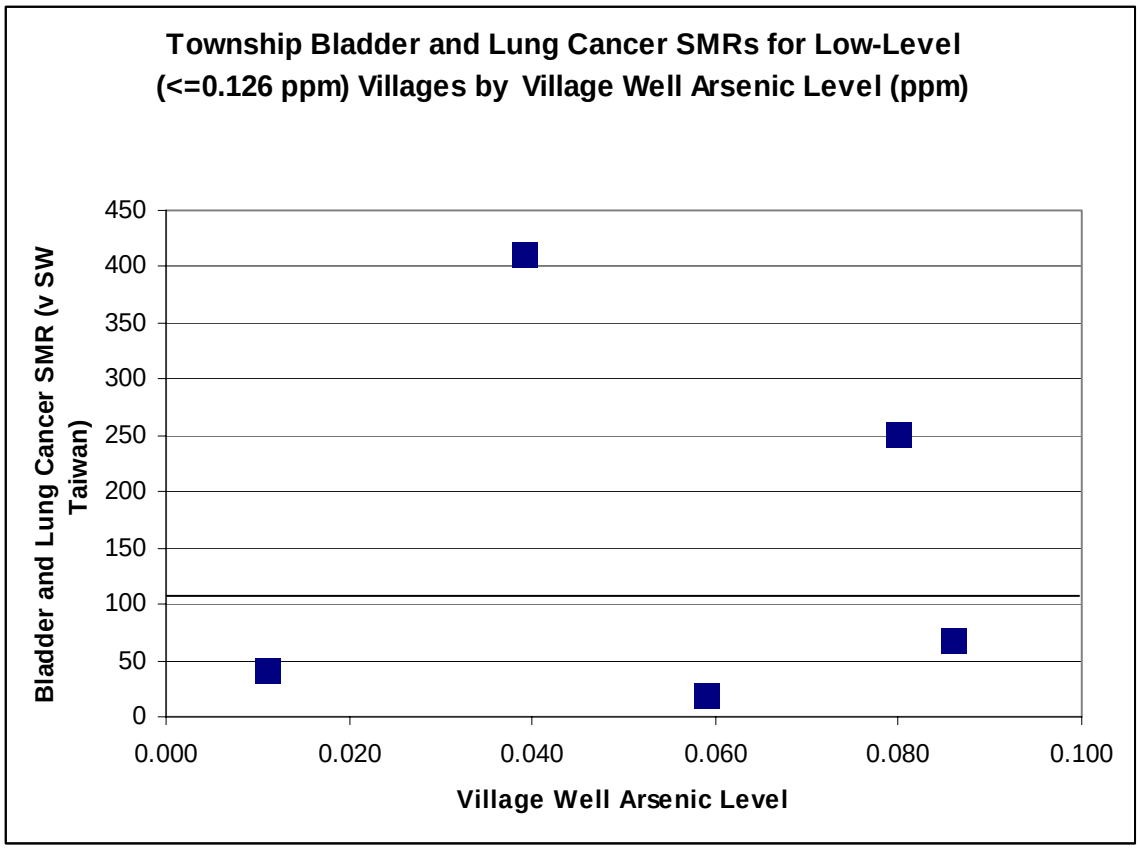
Clearly, there is a "Township Factor" related to Townships 3 and O that dominates the risk of bladder and lung cancer in the low exposure level villages that has not been previously identified in this data set. The risk estimate for the eight villages not apparently affected by the "Township" factor is an SMR of 57 with a 95 % confidence interval of (36-86). Thus, the risk of bladder and lung cancer is significantly low in the low exposure level townships without the "Township Factor."

We do not know the nature of the "Township factor." We do not know the identity of these townships. We do speculate that they may be the Townships of Peimen and Hseuechia, which were previously known to have the highest BFD disease prevalence and bladder cancer mortality among these six townships. Whatever the nature of this "Township Factor", our analysis has demonstrated an example of a spurious factor affecting the risk picture. We suspect that it is not the only such factor in this data set.

Previous analyses have pointed out that there was a geographical risk factor of about 7-10 fold mortality rate (not ratio) that seemed to be greater than the arsenic risk factor. It appears now that, at least in part, that is limited to a few specific townships.

In Figure 9, we have examined to see whether the "Township Factor" is another name for this arsenic exposure. Figure 9 presents the township bladder and lung cancer SMRs with the mean arsenic level by township for the village medians. The mean arsenic levels across these townships range from 0.01 ppm to 0.09 ppm. The townships with high risk are no more likely to be toward the high end of this range than to the low end. There is no indication that the 5-8 fold risk factor is a surrogate for well water arsenic level.

Figure 9: Township-Specific Bladder and Lung Cancer (Combined) SMR for Low-Level (<= 0.126 ppm) Villages by Mean Arsenic Well Level



Analysis of variance (ANOVA) of the bladder and lung cancer SMRs for the eighteen villages showed township to be a significant determinant ($p = 0.002$) and median village well arsenic not ($p = 0.19$). The SW-Taiwan dataset reflects significant inherent geographically-based risk factor(s) which, when disentangled, reveal no significant arsenic-dependent risk for bladder and lung cancers for the low-level exposure villages.

Since the publication and analysis of this SW-Taiwan dataset, additional datasets have been identified that are probably of sufficient power to examine for carcinogenic effects from low-level arsenic exposures. It would be appropriate to investigate those datasets.

Alternative Datasets

We have identified two alternative data sources that might be used for estimating cancer risk in humans from the ingestion of arsenic at low-levels.

Ecological dataset

Lamm et al. (2004) published an ecological analysis that related county-specific median groundwater arsenic levels with county-specific age-adjusted bladder cancer mortality rates for 133 US counties whose population's drinking water supply can entirely from groundwater. The arsenic measurement database is that of the United States Geological Survey (USGS); the mortality data is from the National Cancer Institute. Like all ecological studies (including the SW-Taiwan study), the major limitation of this dataset is not knowing that the median groundwater arsenic concentration is the water that the residents drank. That is unknowable and yields a fundamental limitation. The published study used mortality data from 1950-79. More recent mortality data from US counties is available publicly on the National Center for Health Statistics (NCHS) website.

The Lamm analysis did not find an increased risk of bladder cancer mortality with increased arsenic exposure. In the absence of a positive finding in the database, the usual conditions for performing a quantitative risk analysis are not met. However, Crump and Gibbs (2005) have recently published a methodology for calculating a benchmark dose from a study with no positive finding, demonstrating its utility with data from three human perchlorate studies. EPA might give consideration to using similar analytic methodology with the studies that show no significant positive finding in the exposure range of interest.

Epidemiological dataset

The NRC and the EPA have commented most favorably on the quality and appropriateness of the data from the NE-Taiwan prospective study. The first study published from this data base was the Chiou et al. (2001) study of urinary cancer. NRC (2001) commented (page 67) that this study represented a valuable contribution to the epidemiological database that addresses cancer risk from arsenic in drinking water, although limited at that time by study size. The 2001 study include data from about 3.5 years of follow-up. Chen CL et al. (2004) published data on lung cancer from this study with 7 years of follow-up (through December 31, 2000). While not yet published, follow-up is now probably complete through 2003.

This dataset has the advantage, compared to the Morales and Wu dataset, that it is prospective in nature and will grow in power and sensitivity and that it has individualized data on dosage, health habits (e.g., cigarette smoking) and demographic variables. It is likely to be the most powerful and cleanest dataset for carcinogenic risk assessment of arsenic ingestion. It is the only epidemiological dataset (i.e., with individualized data on exposure, outcome, and potential confounders) that we are aware of that is not confounded with extraneous factors in the Blackfoot Disease endemic area.

Conclusions:

- The SW-Taiwan dataset as presently constructed should not be used for estimation of carcinogenic risk from the ingestion of arsenic. It is not the most appropriate dataset, particularly at low exposure levels. There is too much unknown about the set of risk factors within the study for its use.

- Analysis has already demonstrated the apparent presence of artesian well use, availability of multiple wells, and township as other significant risk markers. These analyses may simply reflect some other unknown risk factor (possibly related to or in parallel with the endemic of Blackfoot disease), but they interfere with the ability to understand the impact of arsenic ingestion on the cancer mortality. The analyses, as presented, do not take into account the explanatory variables that have previously been shown to be significant in the dataset from which this study set was developed.

- Exposures in the range of ~100 ug/L and lower are the exposures of interest in the US. A number of recent studies have reported cancer risk analysis in that exposure range. They should be analyzed as a group.

- If an ecological study in the range of interest is desired, then the data are available for analysis from US government sources. These data would obviate the need to make speculative assumptions of differences in body weight, fluid consumption, nutritional status, etc. between the study population and the US population.

- Epidemiological studies trump ecological studies for risk analysis, if they have sufficient power. The NE-Taiwan study should now have sufficient power and clarity in its data to satisfy the analytics needs of EPA. We recommend that the NE-Taiwan database be explored for use as the primary dataset for the estimation of the carcinogenic risk from arsenic ingestion.

We advise that the SW-Taiwan dataset as presently constructed not be used for the estimation of the human carcinogenic risk from the ingestion of arsenic. We recommend that the NE-Taiwan database be explored for use as the primary dataset and that other studies, particularly the US studies, be examined for their consistency with the findings derived from the NE-Taiwan database.

Thank you for taking the time to reflect upon our analyses. We look forward to being available for questions at the September 12-13, 2005 meeting.

Cordially,

Steven H. Lamm, MD, DTPH
Arnold Engel, MD, MPH
Cecilia Penn, MD, MPH
Rusan Chen, PhD
Manning Feinleib, MD, MPH
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Attachment:

Crump KS and Gibbs JP. Benchmark Calculations for Perchlorate from Three Human Cohorts. Environmental Health Perspectives, 2005 August;113(8):1001-1008.